Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Risk reduction of prostate cancer with drugs or nutritional supplements.

Bibliographic Source(s)

Fleshner N, Ivers N, Lukka H, Shayegan B, Walker-Dilks C, Winquist E, Genitourinary Cancer Disease Site Group. Risk reduction of prostate cancer with drugs or nutritional supplements. Toronto (ON): Cancer Care Ontario (CCO); 2012 May 17. Various p. (Evidence-based series; no. 3-3). [75 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendation 1

In men who are being assessed and monitored for prostate cancer, it is reasonable to offer 5-alpha-reducatase inhibitor (5-ARI) therapy if:

1. They are ≥50 years of age with a normal prostate-specific antigen (PSA) level or
2. They have an elevated PSA level (2.5 to 10 ng/mL) and a negative result on prostate biopsy or
3. They have moderately symptomatic benign prostatic hyperplasia (BPH)

in order to reduce the risk of needing definitive treatment for prostate cancer.

Men who meet these criteria should discuss the pros and cons of this option with their physician. 5-ARI therapy is not being recommended on a population-wide scale.

Recommendation 2

Vitamin E and selenium should not be used to reduce prostate cancer risk.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Prostate cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Clinical Specialty

Family Practice

Internal Medicine

Oncology

Preventive Medicine

Urology

Intended Users

Patients

Physicians

Guideline Objective(s)

To evaluate the effectiveness of drugs and nutritional supplements in reducing the risk of prostate cancer and prostate cancer-related death in patients without a diagnosis of prostate cancer

Target Population

Men older than or equal to 18 years of age who are being assessed and monitored for prostate cancer

Interventions and Practices Considered

1. 5-alpha-reducatase inhibitor (5-ARI) therapy
2. Vitamin E and selenium nutritional supplements (not recommended to reduce prostate cancer risk)

Major Outcomes Considered

- Prostate cancer risk reduction

- Rate of prostate cancer
- Adverse effects of treatment
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

A literature search was performed to identify published studies specifically addressing the prevention of prostate cancer. Searches were run in MEDLINE (1950 to 17 October 2011), EMBASE (1980 to 17 October 2011), and the Cochrane Library (April 2011). Relevant abstracts were searched in the conference proceedings of the American Society of Clinical Oncology (ASCO), the American Urological Association (AUA), and the European Association of Urology for the past three years. Relevant practice guidelines, technology assessments, and systematic reviews were searched in the U.S. National Guideline Clearinghouse, the U.K. National Institute for Health and Care Excellence, the Canadian Partnership Against Cancer - Cancer Guidelines Resource Centre, Canadian Medical Association (CMA) Infobase, and the U.K. National Institute for Health Research - Health Technology Assessment Programme. Reference lists of relevant articles were scanned, and experts in the field were consulted.

Study Selection Criteria

The literature searches were designed to retrieve English-language systematic reviews, meta-analyses, randomized controlled trials (RCTs), and clinical practice guidelines that evaluated drugs or nutritional supplements for the prevention of prostate cancer. RCTs had to include 50 or more patients. Systematic reviews and meta-analyses had to include a detailed description of the review methods (literature search, study selection, and data extraction) in the text of the article and one or more RCTs meeting the above criteria. Studies of healthy volunteers and patients at risk for prostate cancer (e.g., patients with high-grade prostatic intraepithelial neoplasia [HGPIN]) were eligible for inclusion.

Studies and reviews were excluded if the outcome was recurrence of prostate cancer. Studies were also excluded if the intervention focused on diet modification or healthy lifestyle (e.g., consumption of foods rich in certain vitamins or minerals, exercise, other non-drug interventions) rather than on taking specific drugs or supplements.

All studies identified by the literature search were assessed against the selection criteria by three reviewers. Discrepancies regarding eligibility were resolved by consensus.

Appendix 1 of the original guideline document contains a summary of the search strategies conducted in MEDLINE and EMBASE and Appendix 2 provides a flow chart of the search process.

Number of Source Documents

A total of 35 articles met the inclusion criteria: one practice guideline, 13 systematic reviews, and 21 randomized controlled trials (RCTs) (16 full publications and five abstracts). See Appendix 2 in the original guideline document for a flow chart of the search process. The 13 systematic reviews encompassed 32 reports of 25 RCTs (see Appendix 3 in the original guideline document).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Appraisal

The methodological quality of the eligible studies was assessed by the same three reviewers. The A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool was applied to evaluate the systematic reviews. The randomized controlled trials (RCTs) were examined with respect to indicators of methodological rigour, including random allocation, allocation concealment, blinding, handling of patient withdrawals and dropouts, and intention-to-treat analysis.

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument was applied to any clinical practice guidelines that met the inclusion criteria. The AGREE Instrument evaluates the process of practice guideline development and the quality of reporting. The Standards and Guidelines Evidence (SAGE) Inventory of Cancer Guidelines (http://www.cancerguidelines.ca/Guidelines/inventory/index.php) was checked because AGREE II scores are included for all guidelines in the inventory. The Inventory of Cancer Guidelines is a searchable database of over 1,100 English language cancer control guidelines and standards released since 2003, developed and maintained by the Canadian Partnership Against Cancer's Capacity Enhancement Program.

Synthesizing the Evidence

When two or more trials provided appropriate data on outcomes of interest, statistical pooling using meta-analysis was done using Review Manager software (RevMan 5.1) provided by the Cochrane Collaboration. A random effects model was used for all pooling, because it provides a more conservative estimate. Pooled results are expressed as relative risks (RRs) with 95% confidence intervals (CIs). An RR of less than one favours the drug/supplement, and an RR of greater than one favours the placebo or control intervention.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-Based Series (EBS) guidelines developed by the Cancer Care Ontario Program in Evidence-Based Care (CCO PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Genitourinary Disease Site Group (GU DSG) and one methodologist.

The body of evidence in this review is primarily comprised of systematic reviews and mature randomized controlled trials (RCTs). That evidence forms the basis of the recommendations developed by the GU DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada.

Development and Internal Review

The series is a convenient and up-to-date source of the best available evidence on reduction of prostate cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GU DSG is comprised of medical and radiation oncologists, urologists, and pathologists with expertise in GU cancer, plus a lay representative and a methodologist. Review of the document by members of the DSG was generally positive. There were some requests for clearer wording in the first recommendation.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP) Review and Approval

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) RAP, a panel that includes oncologists and whose members have clinical and methodological expertise.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, the Genitourinary Disease Site Group (GU DSG) circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, nine targeted peer reviewers from Ontario and the United States who were considered to be clinical and/or methodological experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out November 3, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Urologists, oncologists specializing in genitourinary cancers, and primary care providers in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base

(Section 2 in the original guideline document). The notification email was sent on November 4, 2011. The consultation period ended on December 15, 2011. The Working Group reviewed the results of the survey.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the RAP of the PEBC.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by a clinical practice guideline, systematic reviews, and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Two randomized controlled trials (RCTs) (44,000 person years of exposure) showed a pooled relative risk reduction for local, biopsy-confirmed prostate cancer of 23% (95% confidence interval [CI], 18 to 27) and number needed to treat (NNT) of 18 (95% CI, 15 to 23).
    - One RCT comparing finasteride, 5 mg/d, with placebo (n=18,882), showed a relative risk reduction of 25% (95% CI, 19 to 31) in the period prevalence of prostate cancer over seven years, with an NNT of 17 (95% CI, 13 to 23). Removing those diagnosed by protocol-mandated biopsy from analysis resulted in a relative risk reduction of 10% (95% CI, 0.09 to 19) and an NNT of 34 (95% CI, 17 to 4,202).
    - One RCT comparing dutasteride, 0.5 mg/d, with placebo (n=8,231), showed a relative risk reduction of 23% (95% CI, 15 to 30) in the incidence of prostate cancer over four years, with an NNT of 20 (95% CI, 15 to 32) (2).
- Meta-analysis of six trials (n=12,857) comparing 5-alpha-reducatase inhibitors (5-ARIs) with placebo/non-5-ARIs in men with benign prostatic hyperplasia (BPH) showed a relative risk reduction of 29% (95% CI, 8 to 46) in the period prevalence of prostate cancer, with an NNT of 104 (95% CI, 66 to 375).

Potential Harms

5-Alpha-Rducatase Inhibitors (5-ARIs)

- There may be a small increased risk of high-grade prostate cancer with 5-ARI therapy. The pooled number needed to harm for high-grade (Gleason score 8 to 10) prostate cancer for two randomized controlled trials (RCTs) was 134 (95% confidence interval [CI], 77 to 293). Alternatively, this could represent a detection bias related to a more effective detection of these cancers in men on 5-ARIs. Nevertheless, the magnitude of this risk, if real, is likely outweighed by the benefits of avoiding overtreatment for biologically insignificant prostate cancer, especially given that these men should be closely monitored.
- As the risk of sexual dysfunction increases with age as well as with 5-ARI therapy, sexual dysfunction rates may be perceived to be higher in clinical practice than when reported in the RCTs. Men should be explicitly asked about such side effects and the risk-benefit ratio of 5-ARI therapy reconsidered if sexual dysfunction is concerning to the patient.

See the "Adverse Effects" sections of the original guideline document for more information.

Qualifying Statements

Qualifying Statements

- It is important for the user to recognize that the recommendation simply urges that it is worth a conversation about the use of 5-alpha-

reducatase inhibitor (5-ARI) therapy between a man (who meets the above criteria) and his physician.

- It is important to acknowledge that the recommendations received mixed reviews from clinicians who participated in the external review of this document (see Section 3 in the original guideline document).
- The user must consider their view of what constitutes "worthwhile" cancer risk reduction when reading this recommendation. Ideally, drugs effective for prostate cancer risk reduction would be offered only to individuals at high risk for fatal forms of the disease. Currently, such knowledge is lacking, and so different perspectives on the value and application of imperfect drugs such as 5-ARIs is expected. Three perspectives are of specific relevance. First, as none of the randomized controlled trials (RCTs) of 5-ARI therapy reported any reduction in overall or prostate cancer-specific mortality, 5-ARI therapy must be considered an unproven intervention from this perspective. Second, as two large RCTs of 5-ARI therapy both reported a small but real increase in higher grade prostate cancers, 5-ARI therapy could be considered ineffective from the perspective of the "first do no harm" principle. A third perspective argues that the observation of more high-grade cancers is due to detection artefacts not 5-ARI therapy. This guideline recommendation offers an alternative perspective that the value of drug therapy for prostate cancer risk reduction should consider the contemporary clinical context. 5-ARI therapy may be worthwhile to reduce prostate cancer risk in a clinical context where case finding is routine due to screening; aggressive anticancer treatment (with uncertain benefits and certain risks) is routinely pursued by and offered to patients; and uncertainties regarding the safety and efficacy of more conservative approaches such as surveillance remain. From this perspective, the recommendation considers the current risk of being "overtreated" for prostate cancer as easily exceeding the small risk associated with developing a high-grade (and still potentially curable) cancer due to 5-ARI therapy.
- The Genitourinary Disease Site Group (GU DSG) recognizes the challenge of weighing this complex set of benefits and risks for each patient. Formal decision aids would be useful to help patients and providers make shared, informed decisions on the use of 5-ARIs for the reduction of prostate cancer. A decision aid on the use of finasteride is available from the American Society for Clinical Oncology: providers and patients may benefit from using this until a revised version is developed that includes all the data synthesized in this review.
- 5-ARI therapy has been shown to reduce the risk of less aggressive prostate cancer (pooled number needed to treat [NNT] for detection of one less prostate cancer during the period of the studies=18), but not to reduce prostate cancer mortality or overall mortality. Currently, many men with slower progressing prostate cancer are treated with surgery or radiotherapy even though such treatment may not be necessary. The GU DSG highly values reducing the number of men treated in this aggressive manner and, therefore, considers the above recommendation reasonable. If the ability and willingness to precisely identify and observe men with biologically indolent prostate cancers emerges in the future, these recommendations would need to be re-evaluated.
- 5-ARI chemoprevention for men without benign prostatic hyperplasia (BPH) should only be considered for those who have initially decided to pursue regular monitoring for prostate cancer development, with the PSA test based on an informed choice regarding risks and benefits, and for those who are committed to ongoing monitoring. The NNT to prevent detection of one case of prostate cancer was higher in this group (NNT=94). Although the optimal monitoring schedule for men receiving 5-ARI therapy to reduce their risk of prostate cancer is uncertain, evidence from the Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trials suggests that they should visit their clinic every six to 12 months for PSA and digital rectal examination (DRE) testing and assessment of medical symptoms and side effects. A low threshold for prostate biopsy in the presence of rising PSA, abnormal DRE, or clinical concerns of the treating physician is appropriate.
- The optimal 5-ARI regimen and duration of therapy are uncertain. In the primary RCTs considered, finasteride 5.0 mg orally (po) daily was given for a planned seven years and dutasteride 0.5 mg po was given daily for four years.
- The expected NNT in clinical practice will likely be much higher, as the diagnosis of prostate cancer in men without BPH was usually made by protocol-mandated prostate biopsy and not for suspicion of prostate cancer.
- Potential recipients of 5-ARI therapy should be well informed about the potential risks. There may be a small increased risk of high-grade prostate cancer with 5-ARI therapy. The pooled number needed to harm for high-grade (Gleason score 8 to 10) prostate cancer for the two RCTs was 134 (95% confidence interval [CI], 77 to 293). Alternatively, this could represent a detection bias related to a more effective detection of these cancers in men on 5-ARIs. Nevertheless, the magnitude of this risk, if real, is likely outweighed by the benefits of avoiding overtreatment for biologically insignificant prostate cancer, especially given that these men should be closely monitored.
- As the risk of sexual dysfunction increases with age as well as with 5-ARI therapy, sexual dysfunction rates may be perceived to be higher in clinical practice than when reported in the RCTs. Men should be explicitly asked about such side effects and the risk-benefit ratio of 5-ARI therapy reconsidered if sexual dysfunction is concerning to the patient.
- 5-ARI chemoprevention is inappropriate in men with limited life expectancy and/or substantial comorbid conditions for whom definitive treatment of prostate cancer would not be pursued.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Fleshner N, Ivers N, Lukka H, Shayegan B, Walker-Dilks C, Winquist E, Genitourinary Cancer Disease Site Group. Risk reduction of prostate cancer with drugs or nutritional supplements. Toronto (ON): Cancer Care Ontario (CCO); 2012 May 17. Various p. (Evidence-based series; no. 3-3). [75 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 May 17

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Genitourinary Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Genitourinary Disease Site Group (GU DSG) members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Neil Fleshner

- Grant/support as principal or co-investigator: Unrestricted educational grant from GSK
- Principal investigator for a clinical trial involving the topic: GSK supported clinical trials – REDEEM and REDUCE
- Published on the topic: GU ASCO Meeting Feb 2011: Abstract Submission ID: 72231 Abstract Title: Effect of dutasteride on prostate cancer progression and cancer diagnosis on rebiopsy in the REDEEM active surveillance study; Fleshner NE, Kapusta L, Donnelly B, Tanguay S, Chin J, Hersey K, Farley A, Jansz K, Siemens DR, Trpkov K, Lacombe L, Gleave M, Tu D, Parulekar WR. Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-e, soy, and selenium. J Clin Oncol. 2011 Jun 10;29(17):2386-90.

Jack Barkin

- Grant support: Researcher/investigator for CombAT, REDUCE and REDEEM trials sponsored by GSK

All other Working Group members and GU DSG members declared no conflict of interest.

Report Approval Panel

All Report Approval Panel members declared no conflict of interest.

External Reviewers

- One external reviewer declared ≥$5000.00 in a single year to act in a consulting capacity for the US Prostate, Lung, Colon, and Ovary Screening Trial (Division of Cancer Prevention, National Cancer Institute, Bethesda, MD) and has published extensively on screening, including prostate cancer screening.
- One reviewer has published extensively on chemoprevention of prostate cancer.
- One external reviewer declared ≥$5000.00 in a single year to act in a consulting capacity for Sanofi International Strategy Board, received grants as a principal or co-investigator from Eli Lilly, and had managerial responsibility for an organization that has received ≥$5000.00 in a single year from a relevant business entity.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Risk reduction of prostate cancer with drugs or nutritional supplements. Summary. Toronto (ON): Cancer Care Ontario (CCO). 2012 May 17. 9 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.
- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 6, 2013.

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Readers with questions regarding guideline content are directed to contact the guideline developer.